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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 10/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/881,012	GINNS ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sh t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 15-26* is/are pending in the application.

4a) Of the above claim(s) *13,14 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 15-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed July 22, 2003. Currently, claims 1-27 are pending. Claims 13, 14, 27 have been withdrawn as drawn to non-elected subject matter.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.

3. Any objections and rejections not reiterated below are hereby withdrawn.

Priority

4. This application claims priority to 09/175,158, filed October 19, 1998 and provisional application 60/062,924, filed October 20, 1997.

The first line of the specification discusses related applications which are not priority documents.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Response to Arguments

The response asserts the first line of the specification has been properly amended to indicate the claim to priority. This argument has been reviewed but is not convincing because the specification does not appear to be amended.

Thus for the reasons above and those already of record, the objection is maintained.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-12, 15-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for analyzing an individual for a genotype associated with BAD in a family affected by bipolar disorder by determining a lod score of a microsatellite marker between D4S394 and DRD5, does not reasonably provide enablement for determining the genotype of any marker within any of the three recited regions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are not enabled by the specification because the specification does not provide sufficient guidance to enable the skilled artisan to determine genotype which are associated with increased or decreased resistance to bipolar affective disorder without undue experimentation for the reasons which follow.

The claims are broadly drawn to methods for determining whether a genotype is associated with increased or decreased resistance to bipolar disorder in a family by determining the genotype of a family member in the region between D4S402 and D4S424 or between D4S431 and D4S404 or between D11S394 and D11S29. The

claimed method is drawn to a method of looking for markers associated with susceptibility or resistance to bipolar affective disorder (BPAD) by looking in three specifically recited regions, one on chromosome 4p, on chromosome 4q and one on chromosome 11.

The specification teaches that a genome-wide search using DNA from patients with bipolar disease was performed with 55 markers (page 34) and regions which gave lod scores higher than 2.0 were considered to be linked. Markers at S13S1 (13q13), D15S45 (15q111-qter) and D6S7 (6pter-p24) were found to have the highest statistical linkage but the specification acknowledges that none of the markers provided a lod score of 3.0 or greater. The specification then teaches that the Old Amish Order was used to perform a genetic epidemiological study of bipolar affective disorder. Genomic DNA was used from individuals from this pedigree to perform a genome wide scan and to look for evidence for regions linked to mental health wellness. The specification teaches that linkage was found with markers on 4p (D4S2949) which is located in the region previously identified by Blackwood to contain a bipolar susceptibility locus and two makers for chromosome 11q (page 44). The specification teaches that the subpedigress were genotyped using additional markers in the 4p region and linkage with mental wellness was analyzed. The specification provides Tables of data but no clear explanation that the data in the tables demonstrate that a protective allele for bipolar affective disorder lies in the 4p or 4q regions. The specification suggests that it is possible and would make sense that there are susceptibility and protective alleles but

does not provide sufficient evidence to establish that such an allele exists between the recited markers.

Blackwood et al (Nature Genetics, Vol. 12, pages 427-430, April 1996) teaches identifying locus associated with bipolar affective disorder. Blackwood teaches carrying out a linkage study in twelve bipolar families (abstract). In a single family a genome search employing 193 markers indicated linkage on chromosome 4p where the marker D4S394 generated a two-point lod score of 4.1 (limitations of Claim 6, 7, 23). Blackwood teaches eleven markers gave positive lod scores including D4S394, D4S1582, D4S1605, D4S1599 and D4S403 (page 427, col. 2, para 1). Table 1 provides a detailed analysis of various locus and the LOD scores (page 429). As described in the Methods section, bipolar families were ascertained and the bipolar status of the individuals in the family were ascertained. DNA was extracted from whole blood, amplified, and gel analysis of microsatellite was performed (page 430, col. 1)(limitations of Claim 12, 15, 16). The analysis was performed by analyzing allele frequencies from the family data (page 430, col. 1)(limitations of Claim 17-19, 21-22). Based upon the data of Blackwood, the markers, for example D4S394 are not associated with increased resistance. In fact, Blackwood illustrates no resistance, but rather a susceptibility locus.

With regard to the region on chromosome 11, the specification fails to provide the LOD score within the region. The specification teaches that "six markers showed linkage" including D11S146. The specification fails to provide any information regarding

the region between D11S394-S11S29. The art fails to teach any associations between bipolar affective disorder and markers on chromosome 11.

The evidence provided in the specification is not sufficient to enable the skilled artisan to use the claimed method because the correlation between decreased risk for BPAD and the recited markers on chromosome 4 has not been established. The specification and the paper by Ginns et al. (PNAS, Vol. 95, pages 15531-15536, December 1998) does not provide data to establish that there is predictable linkage between the regions recited in the claims. At best the specification states that there was linkage for D4S2949 on 4p and D4S397 on 4q but does not establish that makers between the recited markers are predictably linked. The art teaches that the linkage of markers to bipolar disease is highly unpredictable due to the evidence that a number of different genes appear to be involved in this disease. Berrettini (J. Affective Disorders, Vol. 50, pages 287-297, 1998) teaches that the art has given conflicting report for linkage of particular chromosomal regions and susceptibility. Berrettini also discusses that linkage may only be inferred when the LOD score is greater than 3. Berrettini discusses several linkage studies which have described linkage, however, after further analysis, the linkage has not been able to be confirmed. For example, Egeland described a linkage study of Old Order Amish pedigrees with evidence for a bipolar disorder locus on 11p15, but the finding has been weakened by failure to confirm this putative locus in other populations. Similarly, Xq28 was reported to be linked, however, independent investigators have not confirmed the Xq28 linkage (page 289, col 2). As

an example, Berrettini cite the initial linkage statistic as found in Blackwood, and the subsequent confirmation of 4p16 to satisfy generally accepted criteria for valid linkage.

The ability to screen for a wellness allele is even more unpredictable because it is very difficult to distinguish between the presence of a protective allele and the absence of a susceptibility allele. Furthermore, the claims are drawn to a method for looking for a susceptibility or a resistance genotype but the skilled artisan would be unable to predict which makers are linked to susceptibility or resistance based upon the linkage of a single marker within a large region. Extensive experimentation with no predictable results would be required of the skilled artisan to determine the markers which are associated with susceptibility or resistance to BPAD. Berrettini teaches that verification by a second investigating group is required because of the high variability in results that have been observed. Consequently, the skilled artisan would be required to perform undue experimentation to make and use the claimed method.

The specification fails to enable any marker within the recited regions. Markers as defined by the instant specification are "polymorphic locus that serves to identify a unique locus on a chromosome." Markers therefore include but are not limited to microsatellite markers, restriction fragment length polymorphisms, translocations, mutations, deletions, single nucleotide polymorphisms, for example. The skilled artisan would be required to perform additional experimentation to practice the claimed invention as broadly as claimed. While one could conduct additional experimentation to determine whether markers exist within the recited regions on chromosome 4 and 11 and these newly discovered markers are associated with BPAD, the outcome of such

research cannot be predicted, and such further research and experimentation are both unpredictable and undue. It is unpredictable as to whether any quantity of experimentation would allow one to practice the claimed invention.

Additionally, as required by the instant claims, a method for determining a genotype associated with increased or decreased resistance is not predictable given the association in a single individual. As provided by Berrettini, the testing requires large populations and confirmation. The claim appears to assert that the finding of an association in a single member of a family with bipolar affective disorder would suggest a method for determining a genotype. This method however results in unpredictable results which would require further experimentation and confirmation to obtain a reliable result for which a skilled artisan would determine a genotype with an association. Therefore, as written, the method is merely a research design which is intended to determine whether a genotype is associated with increased or decreased resistance and not directed to the result itself. The claim is merely drawn to a method which in itself requires further experimentation with unpredictable results.

Therefore, as written, the skilled artisan would be unable to practice the claimed invention as broadly as claimed with out further unpredictable experimentation.

Response to Arguments

The response traverses the rejection. The response asserts that the examiner has misunderstood the claimed invention, as the claims are directed to methods rather than genotypes associated with increased or decreased resistance to bipolar disease. This argument has been reviewed but is not convincing because absent teachings of

the genotypes, the skilled artisan would be unable to perform the claimed methods. Thus, the genotype discussed by the claims is essential to the functioning of the method. Therefore, the examiner's position is without the presence and description of the genotype, the skilled artisan would be unable to practice the claimed methods.

The response asserts that there is statistically significant linkage to ether susceptibility to BPAD or resistance to BPAD. This argument has been thoroughly reviewed, but is not found persuasive because the specification fails to adequately provide enablement and description for the claims as broadly as written. Claim 1 is recently amended to recite increased resistance to BPAD using chromosome 4 and 11.

It is the examiner's position that no data has been provided for the region of chromosome 11 between D11S394 and D11S29, as required by Claim 1. As provided in the original rejection, "the specification provides Tables of data but no clear explanation that the data in the tables demonstrate that a protective allele for bipolar affective disorder lies in the 4q or 4q regions. The specification suggests that it is possible and would make sense that there are susceptibility and protective alleles but does not provide sufficient evidence to establish that such an allele exists between the recited markers." The response appears to rely on Figure 6, for example to illustrate that the region between D4S431 and D4S404. As seen in Figure 6, there are several microsatellite markers which are not "those markers having a test statistic of $p<0.001$...to show evidence for linkage." For example D4S431 does not appear to have a p-value. D4S394 has a value greater than 0.001, namely 0.0035; D4S1605 has a value of 0.0626. Thus, the region inclusive of D4S431 and D4S404 does not have a

reasonable expectation of having genotypes associated with increased resistance to bipolar disorder. The data offered in Blackwood supports the findings that the region is not associated with resistance, but rather susceptibility (see arguments presented on page 12 of response). It is unclear how a single locus may be both a resistance and a susceptibility locus. The claims are directed to any marker within the region encompassing D4S394 is associated with increased resistance to bipolar affective disorder. There appears to be a conflict between the claims and the data provided in both the specification and the art. Thus the skilled artisan would be required to perform additional experimentation to ascertain whether they may use the claimed invention. It is unpredictable that any amount of experimentation would enable the skilled artisan to use the claimed invention.

With respect to Figure 7, while there is no negative data present, there are only a few data points which have been assayed. Given the results present in Figure 6, it is unpredictable that each microsatellite between the chromosomal regions of D4S402 and D4S424 are associated with BPAD.

With respect to Claim 24and increased susceptibility, D14S148 has a p-value, as shown in Figure 5, as 0.0217 which is larger than the p value asserted by the specification and the response as significant. Moreover, the chromosomal regions on between D6S344 and D6S89 exhibit a significant value only at D6S7 (see Figure 3). Similarly, regions on chromosome 13 between D13S171 and D13S218 only appears significant between D13S1.

The response asserts that one skilled in the art would know if a particular marker has been shown to be linked, makers lying within a span of about 10 cM on either side of the marker represent likely candidates for further markers. This argument has been thoroughly reviewed, but is not found persuasive because it is apparent from Figure 6 and 7 that this is not an accurate predictor of association. The skilled artisan would be required to perform experimentation to determine whether an association does exist since there are several within the range assert which are not associated. It is unpredictable which makers are associated and which markers are not associate with out undue and unpredictable experimentation.

The response acknowledges that the outcome of marker association can not be predicated (page 11, para 3). As noted by Brenner v. Manson, 383 U.S. 519, 535-536 (1996), "Congress intended that no patents be granted on a chemical compound whose sole "utility" consists of its potential role as an object of use-testing...a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion". To the extent that the claims are directed to determining whether markers are associated, the invention was not complete at the time the invention was filed, and would thus constitute a hunting license which is not enabling for a patent.

With respect to the broad term marker and genotype, the specification has not enabled the skilled artisan to use the claimed invention along the broad scope of the terms. Markers as defined by the instant specification are "polymorphic locus that serves to identify a unique locus on a chromosome." Markers therefore include but are

not limited to microsatellite markers, restriction fragment length polymorphisms, translocations, mutations, deletions, single nucleotide polymorphisms, for example.

Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-12, 15-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to the identification of markers which are associated with susceptibility or resistance to BPAD. The specification has provided some preliminary data that a single marker in the 4p region, and a single marker in the 4q region show some evidence for linkage to mental health wellness in the Old Amish Order. However, the claims are broadly drawn to a method of using a large genus of markers which lie in a large region of chromosome 4 and 11, but the specification does not teach that a representative number of markers in this large region are linked to BPAD. A common structural feature has not been identified such that the skilled artisan would know that all markers in this region are linked or which specific markers within the recited regions are linked.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

The specification fails to describe a representative number of markers within the recited regions of chromosome 4 and 11. Moreover, the specification fails to describe a representative number of markers within the recited regions of chromosome 4 and 11 which are associated with an increased or decreased resistance to familial bipolar affective disorder. Markers as defined by the instant specification are a polymorphic locus that serves to identify a unique locus on a chromosome. Markers therefore include but are not limited to microsatellite markers, restriction fragment length

polymorphisms, translocations, mutations, deletions, single nucleotide polymorphisms, for example. The specification has only described a limited number of microsatellite markers which are not all associated with BAD. The art teaches that there are about 20 cM between markers D4S402 and D4S42 and about 20 cM between markers D4S431 and D4S404. These regions are extremely large and contain millions of base pairs. The specification has not described a representative number of markers from the numerous types of markers know, such as microsatellite markers, SNPs, deletions, insertions which are associated in the very large regions on chromosomes 4 and 11.

Therefore, the specification has not sufficiently described the essential features of the claimed invention.

Response to Arguments

The response traverses the rejection. The response asserts the specification has provided written description because the specification provides eve more than a "representative number" of markers within each of the claimed regions of the chromosomes. This argument has been reviewed but is not convincing because the term markers, as discussed above, "markers as defined by the instant specification are a polymorphic locus that serves to identify a unique locus on a chromosome. Markers therefore include but are not limited to microsatellite markers, restriction fragment length polymorphisms, translocations, mutations, deletions, single nucleotide polymorphisms, for example. The specification has only described a limited number of microsatellite markers which are not all associated with BAD. The art teaches that there are about 20 cM between markers D4S402 and D4S42 and about 20 cM between markers D4S431

and D4S404. These regions are extremely large and contain millions of base pairs. The specification has not described a representative number of markers from the numerous types of markers know, such as microsatellite markers, SNPs, deletions, insertions which are associated in the very large regions on chromosomes 4 and 11." The examiner acknowledges the presence of several microsatellite markers which are within the claimed regions. However, this is not representative of the broad genus of markers claimed.

Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

7. No claims allowable.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg
Jeanine Goldberg
September 30, 2003

JEHANNE SOUAYA
PATENT EXAMINER
Primary

Jehanne Souaya
9/30/03